脳梗塞の再発予防
～最近のエビデンスを踏まえて～

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1．最近のわが国における脳梗塞の動向

脳卒中は現在日本人の死因の第３位を占めているが、脳卒中による死亡の68%は脳梗塞で、かつてもっとも多かった脳出血は現在では23%を占めるに過ぎない、脳卒中の総患者数でみると脳梗塞の占める割合はさらに76%と大きくなり、人口の高齢化とともに今後も脳梗塞患者数の増加が予想されている。

脳卒中の問題点の一つは死には至らなくても後遺症が高頻度に残ることである。最近のわが国における脳梗塞急性期例の退院時の転帰をみても、死亡率は７%と少ないが、日常生活に介助を要する例が32%存在する。寝たきり患者を含めた要介護者の原因疾患の約４割を脳卒中が占め、社会的、経済的にも大きな問題を提起している。

2．脳梗塞の臨床病型

脳梗塞は現在、アテローム血栓性梗塞、ラクナ梗塞、心塞栓性梗塞、その他の脳梗塞の４つの病型に分けられている（表１）。病型によって成因や病態、予後が異なるので急性期治療や再発予防における治療法の選択においても病型に配慮することが重要である。

表１．脳梗塞の臨床病型

	アテローム血栓性梗塞	ラクナ梗塞	心塞栓性梗塞
成因	主幹動脈のアテローム硬化	穿通枝の血管壊死	心内血栓による塞栓
危険因子	高血圧、糖尿病脂質代謝異常、喫煙	高血圧	塞栓源心疾患(心房細動など)
退院時ADL自立*1	63%	89%	63%
急性期死亡率*1	６%	０%	10%

＊１：済生会中央病院データ

最近のわが国における各病型の頻度は、ラクナ梗塞39%、アテローム血栓性梗塞33%、心塞栓性22%、その他６%であった。従来わが国ではラクナ梗塞が約半数を占めるという報告が多かったが、最近はアテローム血栓性梗塞が増加しており、その原因として脳梗塞危険因子としての糖尿病と高脂血症の増加が指摘されている。

3．脳梗塞の再発率と再発予防対策

脳梗塞は再発率が高く、初発例では発症後５年以内に約30%が再発する。特に１年以内の再発率が約10%ともっとも高く、その後は年間５%程度の再発率がある。再発を繰り返すたびにADLの低下が進むので、予防が重要である。

現在、脳梗塞の二次予防対策として有効性が確立されているものを表２にあげる。表２の各対策の（　）内には最近発表されたわが国の脳卒中治療ガイドラインの推奨グレード（表３）を示す。全例に行うべき対策として危険因子の管理が、病型別、病態別に選択する治療法として抗血栓療法、頸動脈内膜剥離術がある。以下、各治療法の概略を述べる。

表２．脳梗塞の二次予防対策

・全症例に行うべき対策：
　危険因子の管理（高血圧(A)，糖尿病(C1)
　高脂血症(C1)，喫煙(C1)，飲酒(C1)，
　肥満(C1)）
・非心原性脳梗塞(アテローム血栓性梗塞と
　ラクナ梗塞)
　抗血小板薬(A):アスピリン(A)，
　　チクロピジン(A),シロスタゾール(B)
・心原性脳塞栓症
　抗凝固薬：ワルファリン(A)
・70%以上の症候性頸動脈狭窄
　頸動脈内膜剥離術(CEA)（A)

表３．脳卒中治療ガイドライン2004

脳卒中のrecommendation gradeに関する委員会の分類

推奨のグレード	内　　容
A	行うよう強く勧められる
B	行うよう勧められる
C1	行うことを考慮しても良いが、十分な科学的根拠がない
C2	化学的根拠がないので、勧められない
D	行わないよう勧められる

（脳卒中合同ガイドライン委員会）

４．危険因子の管理

脳梗塞の危険因子には高血圧、糖尿病、脂質代謝異常、喫煙、飲酒、身体活動の減少、肥満などが知られている。表４にアメリカ心臓協会（AHA）の危険因子の管理目標ガイドラインをあげた。本稿では特に重要な高血圧、糖尿病、脂質代謝異常を取り上げる。

（１）高血圧

高血圧は現在でも脳梗塞のもっとも重要な危険因子である。収縮期血圧、拡張期血圧ともに血圧値が高いほど脳梗塞、脳出血に発症率が高くなり、治療によって血圧を下げることにより脳卒中の発症率を低くできることが、多くの疫学研究、介入研究によって確認されている。また、脳卒中の一次予防には血圧値は低ければ低いほどよいとされる。

表４．虚血性脳卒中二次予防のガイドライン(AHA:1999)

危険因子の管理

危険因子	ゴール
高血圧	臓器障害なし SBP＜140mmHg かつ DBP＜90mmHg
	臓器障害あり SBP＜135mmHg かつ DBP＜85mmHg
喫煙	禁煙
糖尿病	血糖＜126mg／dL
脂質	LDL＜100mg／dL
	HDL＞35mg／dL
	TC＜200mg／dL
	TG＜200mg／dL
アルコール	適度な消費（≦２杯／日）
運動	30－60分、３－４回／週（中等度の運動）
体重	≦理想体重の120%

脳梗塞の二次予防に対しても血圧管理が有効であることを証明した研究にPROGRESS（Perindopril Protection Against Recurrent Stroke Study）がある。PROGRESSでは脳卒中またはTIAの既往のある例がACE阻害薬であるペリンドプリル群とプラセボ群に振り分けられ、その後の脳卒中再発率が比較検討された。４年間の観察の結果、ペリンドプリル群の脳卒中再発率はプラセボ群に比べ28%低かった。しかし、ペリンドプリル単独投与群ではこの差は５%と有意ではなく、ペリンドプリルと利尿薬であるインダパミドを併用した群にのみ有意な差が見られた。(43%の減少)。両群の平均血圧値の差は単独療法群では５／３mmHg、併用療法群では12／５mmHg（いずれもペリンドプリル群で低値）で、両群間の脳卒中減少率の差は血圧降下度の違いによるものと考えられる。この試験はもともとACE阻害薬の脳卒中再発予防効果を検討することが目的であったが、脳卒中の予防には使用する薬剤の種類よりも血

圧をきっちりと下げることがより重要であることを証明した結果となった。

従来、脳梗塞の慢性期には血圧をあまり下げることは好ましくないとされてきた。その理由として脳梗塞患者では脳循環の自動調節域の下限が血圧の高い方（右方）へシフトしているため、血圧を下げ過ぎると脳血流量の減少を招く危険性があると説明されてきた。しかし、最近では血圧値を長期にコントロールすると自動調節域の下限の上方へのシフトは正常化することが確認されており、やはり血圧は十分にコントロールすべきであると考えられるようになっている。ただし、アテローム血栓性梗塞では血圧の下げ過ぎは逆に再発率を増加させるとの報告もあり、再発予防のために血圧はどこまで下げるべきかの結論は得られていない。しかし、少なくとも高血圧の基準である140／90mmHg未満に管理すべきである。

（2）糖尿病

糖尿病も脳梗塞の危険因子であることが多くの疫学研究によって確認されている。また我々の施設のデータでは血糖コントロールの不良な者ほど脳梗塞の発症率が高くなることが明らかであった。しかし、糖尿病患者における治療介入研究であるUKPDS（UK Prospective Diabetes Study）では、血糖コントロールを厳格に行っても脳卒中の発症率は減少しなかった。一方、血圧の厳格な管理により脳卒中発症率は半減し、糖尿病例では脳卒中予防のために、より一層の厳格な血圧管理が重要であることが明らかとなった。

糖尿病例は脳梗塞の再発率も高いことが明らかにされている、再発予防に対する血圧管理や血糖管理の有効性を直接証明した研究はないが、一次予防の成績から考えて、糖尿病例では血圧値の目標として130／85mmHg以下、血糖管理はHbA1c6.5%以下程度をまず目指したい。

（3）脂質代謝異常

脂質代謝異常は冠動脈疾患では重要な危険因子であることが確立されているが、従来脂質代謝異常と脳梗塞の発症率には強い関係はないとする疫学研究が多かった、むしろわが国の古い研究では血清コレステロールの低値が脳出血の危険因子となることが報告されている。

しかし、最近になってコレステロールと脳梗塞の関係が注目されるようになった。それは高脂血症治療薬であるスタチン（HMG CoA還元酵素阻害薬）による冠動脈疾患の予防を目的とした介入研究において、心筋梗塞だけではなく脳梗塞の発症も20～30%減少することが明らかになったためである。シンバスタチンを用いたHPS（Heart Protection Study）では、脳卒中の病型別の発症率を検討した結果、脳梗塞の発症率は30%と有意に減少したのに対し、脳出血の発症率に差はみられず、スタチンによるコレステロール低下が脳出血の危険性を高めることはないとされた。ただし、最近発表されたHPSの脳卒中に関する二次解析の結果では、スタチンの脳卒中の二次予防効果は明らかとはなっていない。

またスタチンにはコレステロール低下作用だけではなく、頸動脈のアテローム硬化の進展や不安定化を抑制する作用があることが多くの研究によって明らかにされており、スタチンによる脳梗塞発症率の減少にはコレステロール低下作用とともにそれ以外の抗アテローム硬化作用が関与している可能性がある。

脳梗塞の再発予防のための血清脂質の管理目標は、日本動脈硬化学会のガイドラインではカテゴリーB4として、TC200mg／dℓ未満、LDL-C120mg／dℓ未満、HDL-C40mg／dℓ以上、中性脂肪150mg／dℓ未満とされている。

5．抗血栓療法

（1）非心原性脳梗塞

心塞栓性梗塞（心原性脳塞栓症）以外の脳梗塞、特にアテローム血栓性脳梗塞の二次予

防には抗血小板薬が有効であることが多くの介入研究によって明らかにされている。これらの血小板薬による介入研究のメタ解析を行っているATT（Antithrombotic Trialist's Collaborations）によれば、TIA、脳梗塞患者における抗血小板薬による二次予防効果は、血管事故（心筋梗塞、脳卒中、血管死）に対して22%、脳卒中だけで25%のオッズ減少とされている。

現在わが国では脳梗塞患者に適応のある抗血小板薬にはアスピリン、チクロピジン、シロスタゾールがある。まず第一選択薬は効果、副作用、薬価などの点から低用量アスピリンとするのが国際的な標準である。チクロピジンはアスピリンよりも二次予防効果は1.2%大きいが、稀に顆粒球減少、血栓性血小板減少性紫斑病（TTP）、肝機能障害などの重篤な副作用が生じるため、わが国では二次選択薬となっている。国際的には同じ系統の薬剤でより副作用の少ないクロピドグレルが二次選択薬の標準になっており、現在わが国でも治験が進められている。

シロスタゾールは閉塞性動脈硬化症（ASO）の治療薬であるが、わが国で行われたプラセボを対照とした脳梗塞の二次予防試験（CSPS:Cilostazol Stroke Prevention Study）の結果、脳梗塞の再発率を約40%減少させることが明らかとなり（表5）、最近脳梗塞の再発予防に対する効能追加が認証された。CSPSではアテローム血栓性梗塞、ラクナ梗塞の病型別の再発予防効果が検討されているが、いずれの病型に対しても等しく有効であることが確認された。従来ラクナ梗塞の再発予防に抗血小板薬が有効であることを証明した研究はなかったので、この結果は臨床的に重要である。

表5．Cilostazol Stroke Prevention Study（CSPS）

	薬剤	総観察年数	年間発症率（%）	相対リスク減少率（%）
全梗塞	シロスタゾール	889.6	3.37	41.7
	プラセボ	986.0	5.78	(P<0.05)
ラクナ梗塞	シロスタゾール	673.8	2.97	43.4
	プラセボ	734.4	5.25	(P<0.05)
アテローム血栓性梗塞	シロスタゾール	109.8	6.37	39.8
	プラセボ	104.0	10.58	

(Jounal of Stroke and Cerebrovascular Disease,2000)

アスピリンは脳梗塞の再発予防に有効であるが、脳出血の発症率も若干高くなることが知られている。我々の施設のデータでは、脳梗塞後に脳出血を発症する例は多発性のラクナ梗塞例に多く、またアスピリンまたはワルファリンなどの抗血栓薬を服用中の患者に多かった。最近MRIのT2*（T2スター）強調画像が脳内の無症候性微小出血の診断に有力であることが指摘されており、またアスピリン服用中に脳出血を発症した例では無症候性微小出血が高頻度にみられることから、脳出血発症の危険を予知する検査法として期待されている。ちなみに前述したCSPSではシロスタゾール群の脳出血発症の危険性が高いと考えられる症例（MRIにおける多発性ラクナ梗塞、脳室周囲の白質病変、微小出血の存在）ではシロスタゾールを第一選択とするのも一つの考えである。

（2）心塞栓性梗塞（心原性脳塞栓症）

心塞栓性梗塞のもっとも重要な塞栓源は高齢者に多い非弁膜症性心房細動（NVAF）である。NVAFのある者は年間約5%の脳卒中発症率があるが、心塞栓性梗塞は脳梗塞の中でももっとも重症となりやすく、現在でも10%の死亡率があり転帰不良なため、その予防は臨床的にきわめて重要である。特に過去にTIAまたは脳卒中の既往のある例では、塞栓症再発の危険は約2.5倍となり、年間発症率は12.5%にも及ぶので、再発予防対策が必須である。

これまでに行われた介入研究によりNVAF例の脳卒中の再発予防にはアスピリンの効果は小さく（脳卒中減少率20%）、ワルファリンによる抗凝固療法が有意に優ることが明らかとなっている（脳卒中減少率60%）。しかし、ワルファリンは用量調節が難しいこと、他の薬剤や食物との干渉

作用が多いことなどから、ガイドラインでは抗凝固療法の適応があるとされる患者でも実際には実施されていないことが少なくない。最近ワルファリンに代わる経口抗凝固薬として抗トロンビン薬であるXimelagatranが注目されている。Ximelagatranは用量調節の必要がなく、また干渉作用も少ないことから、投与が簡便なことが利点である。現在ワルファリンとの比較試験が進行中であるが、これまでのところ期待できる効果が得られており、今後の展開が期待できる。

6．頸動脈内膜剥離術（Carotid endarterectomy:CEA）

頸動脈に70%以上の高度狭窄があり、TIAまたは軽症脳梗塞の既往のある患者では、抗血小板薬だけではなく、それに加えて外科的にCEAを加えた方が脳梗塞の再発予防効果が大きいことが明らかにされている。ただし無症候性頸動脈狭窄に対する手術適応については十分なコンセンサスが得られていない。いずれにしても総頸動脈分岐部から内頸動脈起始部（ほぼ甲状軟骨上縁にあたる）に血管雑音の聞こえる患者では一度は超音波検査を行って高度狭窄の有無を確認しておくべきである。

7．おわりに

脳梗塞の再発予防に対し、すでにその有効性が確立されている治療法を中心に解説した。血圧や脂質の管理など、これまでの医療の常識からは発想の転換が必要と思われる新たな展開がみられていることを理解していただきたい。本小論が実地医家の診療に少しでもお役に立てれば幸いである。

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Aortogenic Embolism Is a Possible Mechanism of Cryptogenic Stroke

Kazuo Kitagawa, MD

I read with great interest the recent article by Bang and colleagues demonstrating the frequency and mechanisms of stroke recurrence after cryptogenic stroke.[1] They suggested that occlusive lesions other than significant stenosis of relevant artery may play an important role in the stroke recurrence in patients with cryptogenic stroke, the stroke with no determined cause. On the basis of clinical findings, brain magnetic resonance imaging (MRI) and angiography, carotid duplex, echocardiogram, and routine blood tests, they divided patients into large artery disease, cardioembolism, small artery disease, and no determined cause categories. In the discussion, they mentioned that more extensive studies should be performed to document possible embolism due to patent foramen ovale and paradoxical embolism with transesophageal echocardiography (TEE). Although Bang and colleagues did not mention it, I want to add aortogenic embolism as a frequent cause for cryptogenic stroke. Amarenco and colleageus[2] and Toyoda and colleageus[3] previously demonstrated significant incidence of aortic complex lesion, a potential embolic source, in ischemic stroke patients with no determined cause. In our consecutive 147 patients with ischemic cerebrovascular disease including ischemic stroke and transient ischemic attacks, 56 patients had aortic complex lesion defined as an aortic intimamedia thickness (IMT) greater than 4mm, mobile plaque, and/or ulcers.[4] Carotid IMT, evaluated by carotid duplex, was closely associated with aortic IMT. Each one standard deviation greater carotid IMT was associated with 4.2-fold higher likelihood of complex aortic lesions. Our results together with others'[5] clearly demonstrated that the patients with mild carotid atherosclerosis were likely to have aortic complex lesions as an embolic source. Therefore, I recommend examination of aortic arch with TEE or MRI in patients with cryptogenic stroke especially when mild stenosis (<50%) is found in extracranial and/or intracranial cerebral artery.

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Cerebral hemodynamics and metabolism in adult moyamoya disease: Comparison of angiographic collateral circulation

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Purpose: The extent of the hemodynamic and metabolic impairments in adult patients with moyamoya disease is still controversial. The aim of the present study was to evaluate the hemodynamic and metabolic status in relation to the development of basal moyamoya vessels (BMVs). ***Methods:*** The cerebral blood flow (CBF), cerebral metabolic rate of oxygen ($CMRO_2$), oxygen extraction fraction (OEF), and cerebral blood volume (CBV) were measured using PET in ten patients with ischemic adult moyamoya disease (mean age, 36.6 years) and six age-matched normal controls (mean age, 33.3 years). The cerebrovascular reserve (CVR) after acetazolamide (ACZ) loading was also estimated using iodine-123 *N*-isopropyl-*p*-iodo amphetamine single photon emission computed tomography (^{123}I-IMP SPECT). ***Results:*** Based on the angiographic findings, eleven cerebral hemispheres with well-developed BMV (extensive BMV hemispheres) and nine cerebral hemispheres with diminished BMV (diminished BMV hemispheres) were identified. The main routes of collateral circulation in extensive BMV hemispheres were BMVs and leptomeningeal anastomoses. On the other hand, in diminished BMV hemispheres, transdural anastomosis was predominant, and leptomeningeal anastomoses were less developed. In cortices distal to the occluded internal carotid artery, the extensive BMV hemispheres exhibited a significantly lower CBF, $CMRO_2$, CBF/CBV, and CVR ($p < 0.05$) and a significantly higher CBV and OEF than in diminished BMV hemispheres and controls ($p < 0.05$). Except for the CBF in the white matter, the mean hemodynamic and metabolic parameters of the diminished BMV hemispheres were not significantly different from those of the controls. ***Conclusion:*** The extensive development of basal moyamoya vessels is a sign of severe hemodynamic impairment in adult patients with ischemic moyamoya disease. The results may not apply to adults with hemorrhagic onset.

Key words: adult moyamoya disease, collateral circulation, PET, cerebral blood flow, cerebral metabolism

INTRODUCTION

MOYAMOYA DISEASE is a cerebrovascular disease characterized by the spontaneous and progressive occlusion of the terminal portion of the bilateral internal carotid arteries (ICA), proximal parts of the anterior cerebral artery (ACA), and the middle cerebral artery (MCA) with a spontaneously developed collateral vascular network.[1–3] Most pediatric patients demonstrate extensive development of basal moyamoya vessels and present with

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Table 1 Patient characteristics

Patient No.	Age y/Sex	Subtype	Major clinical symptoms	Duration from onset of disease	Infarct on MRI
1	31/F	TIA	Weakness of Rt limbs	22 y	Lt WM lacunar
2	37/F	TIA	Weakness of limbs	28 y	Negative
3	21/F	TIA	Syncope	3 mo	Lt WM lacunar
4	37/M	CI	Lt hemianopsia	3 mo	Rt occipital
5	42/F	AS	None	None	Negative
6	47/F	CI	Weakness of Lt limb	3 mo	Rt precentral area
7	29/F	CI	Lt hemianopsia	23 y	Rt parietooccipital
8	35/F	TIA	Weakness of Rt limbs, aphasia	1 mo	Lt LN lacunar
9	32/F	AS	Headache	8 y	BG-WM lacunar
10	50/M	CI	Rt hemianopsia	5 y	Lt occipital

TIA, transient ischemic attack; CI, cerebral infarction; AS, Asymptomatic: indicates asymptomatic carotid artery disease; BG, basal ganglia; WM, white matter; LN, lentiform nucleus; Lt, left; Rt, right.

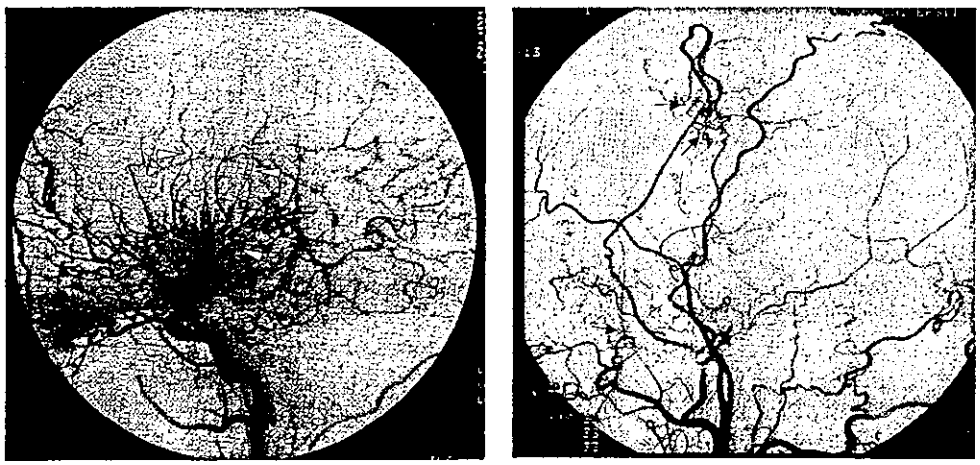

Fig. 1 Representative findings of the cerebral angiography in moyamoya disease. Left panel: Typical angiographic image of extensive basal moyamoya vessels development type. Nether middle-nor anterior cerebral arteries are visible, and moyamoya vessels with retrograde filling of long-penetrating medullary arteries developed (*white arrowhead*). Right panel: Typical angiographic image of diminished basal moyamoya vessels type. Branches of the internal carotid artery and basal moyamoya vessels are not seen. Transdural anastomosis (*arrow*) developed instead.

ischemic events.[4] Previous studies have indicated a decrease in cerebral blood flow (CBF) and CBF in response to carbon dioxide inhalation.[5–7] Compensating mechanisms, such as an increase in cerebral blood volume (CBV) and the oxygen extraction fraction (OEF) have been found in the territory of the occluded arteries.[7] Cerebral oxygen metabolism was maintained in the normal range.[8,9]

In contrast, the severity of the hemodynamic and metabolic impairments in adult patients remains controversial. Kuwabara et al. found no significant reduction in CBF or the cerebral metabolic rate of oxygen ($CMRO_2$) in four adult patients. Misery perfusion was not detected either.[8] Taki et al. found a decrease in the CBF/CBV ratio, an index of perfusion pressure, in nine adult patients.[9] In both of these studies, the $CMRO_2$ did not decrease in the cortical gray matter, basal ganglia, or white matter. On the other hand, Morimoto et al. found a decrease in the cortical CBF and $CMRO_2$ and an increase in the CBV and OEF in five patients who later underwent superficial temporal artery to middle cerebral artery (STA-MCA) bypass surgery.[10] The discrepancies among these studies may be caused partly by a selection bias in the patients, the severity of the primary steno-occlusive ICA lesion, or the development of collateral circulation.

The aim of the present study was to clarify the extent of the hemodynamic and metabolic impairments in adult patients with ischemic moyamoya disease by examining collateral circulation using cerebral angiography. Patients with well-developed basal moyamoya vessels (BMVs) were compared with those with diminished basal moyamoya vessels.

PATIENTS AND METHODS

All the patients were seen at the Osaka University Medical School Hospital between March 2000 and April 2003. Eighteen consecutive patients diagnosed as having moyamoya disease were selected. Pediatric patients, patients with a cerebral infarction measuring more than 3 cm in diameter in the ICA territory (based on magnetic resonance imaging [MRI] images), patients with intracerebral hemorrhage and patients with a history of head surgery were excluded from the study. Patients were also excluded if they had experienced a clinical stroke event within one month prior to the start of the study.

A total of ten patients with moyamoya disease (two males, eight females; mean ± SD age, 36.6 ± 9.1 years, range 21 to 50 years) were finally enrolled in the study. All patients had undergone a digital subtraction angiography (DSA) and MRI examination. Four patients had transient ischemic attacks (TIAs), one patient suffered from headache, one patient had asymptomatic carotid artery disease, and four patients had minor cerebral infarctions. Table 1 shows the clinical features and MRI findings of these ten patients. All patients were clinically diagnosed as definite cases of moyamoya disease based on the *Criteria for the Diagnosis of Moyamoya Disease* (Ministry of Health and Welfare of Japan, 1996).[11] We evaluated the angiographic findings of all 20 hemispheres in the ten patients. The hemispheres were divided into two groups according to the extent of BMV development, extensive BMV with retrograde filling of long-penetrating medullary arteries (extensive BMV group; n = 11 hemispheres), and poor BMV with no retrograde filling of the medullary arteries (diminished BMV group; n = 9 hemispheres) (Fig. 1). Furthermore, the development of leptomeningeal collateral circulation was evaluated using the classification system established by Mugikura et al.[12] The development of leptomeningeal anastomosis was classified into four grades: good, cortical branches in all three (frontal, parietal, and temporal) lobes opacified; moderate, cortical branches in two lobes opacified; poor, cortical branches in one lobe opacified; none, no collateral circulation. Six age-matched normal volunteers (two males and four females, 33.3 ± 6.6 years, range 26 to 43 years) were recruited as a control group. All subjects underwent both PET and iodine-123 *N*-isopropyl-*p*-iodo amphetamine single photon emission computed tomography (^{123}I-IMP SPECT) examinations. A detailed explanation of the purpose of the study and all the procedures used in the study was given prior to the enrollment of the subjects in the study. Written informed consent was obtained from all the subjects. The study was approved by the Ethical Committee of Osaka University.

SPECT Imaging

We used the split-dose ^{123}I-IMP SPECT method.[13] A high-performance, four-head rotating gamma camera (Gamma View SPECT 2000H, Hitachi Medical Co., Tokyo, Japan) was used to perform the SPECT imaging. This gamma camera was equipped with a low-energy, general purpose, parallel-hole collimator with a spatial resolution of 13.0 mm full-width-at-half-maximum (FWHM). Subjects were asked to lie supine on the

Table 2 Development of basal moyamoya vessels and collateral circulation on angiography

	patient No.	side	site of ICA occlusion	leptomeningeal*	transdural
extensive BMV	1	Rt	cavernous	moderate	+
	1	Lt	lacerum	poor	+
	2	Rt	communicating	moderate	+
	2	Lt	communicating	moderate	+
	3	Rt	cavernous	good	−
	3	Lt	cavernous	good	+
	4	Rt	clinoid	poor	+
	4	Lt	ophthalmic	poor	+
	5	Rt	communicating	good	−
	6	Rt	ophthalmic	good	+
	10	Lt	clinoid	good	+
diminished BMV	5	Lt	communicating	none	−
	6	Lt	ophthalmic	none	+
	7	Rt	cavernous	poor	++
	7	Lt	ophthalmic	moderate	++
	8	Rt	communicating	moderate	++
	8	Lt	communicating	moderate	++
	9	Rt	ophthalmic	good	+
	9	Lt	communicating	poor	++
	10	Rt	clinoid	good	+

BMV, basal moyamoya vessels; ICA, internal carotid artery; Lt, left; Rt, right; +, indicates thin collateral; ++, indicates rich collateral; −, none; *, classification of Mugikura et al.

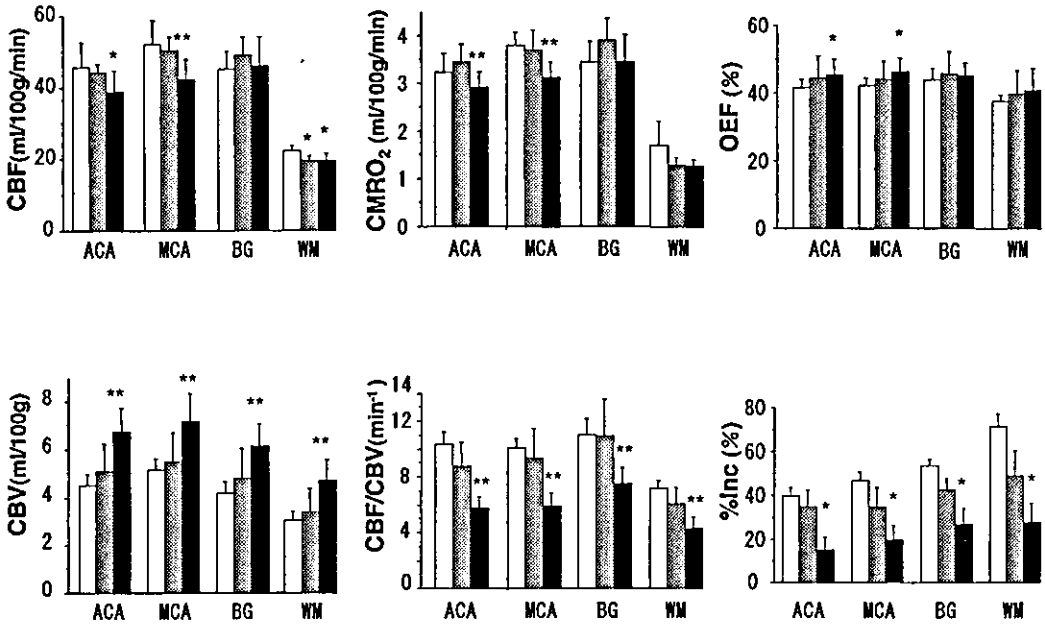

Fig. 2 Comparison of regional cerebral blood flow (CBF), regional cerebral metabolic rate of oxygen ($CMRO_2$), regional oxygen extraction fraction (OEF), regional cerebral blood volume (CBV), regional cerebral blood flow over cerebral blood volume (CBF/CBV), cerebrovascular reserve (CVR) by the angiographic types. Data are show as means plus SD. Open column, hatched column, and closed column indicate normal control, diminished basal moyamoya vessel (BMV) group, and extensive BMV group, respectively. MCA, middle cerebral artery territory; ACA, anterior cerebral artery territory; BG, basal ganglia; WM, white matter; *, $p < 0.05$ vs. normal control; **, $p < 0.05$ vs. normal control and diminished BMV group.

scanner bed with their eyes closed in a dimly lit and quiet room. The subject's head was immobilized using a head holder. A built-in light beam was adjusted to the subject's orbito-meatal (OM) line so that the system would reconstruct images parallel to the OM line. The acquisition started with the intravenous injection of 111 MBq of ^{123}I-IMP (Perfusamine™, Nihon Medi-Physics Co., Ltd., Nishinomiya, Japan). Nine minutes later, 1 g of acetazolamide (ACZ) (Diamox™, Lederle Ltd., Tokyo, Japan) was slowly administrated intravenously. At 27 minutes after the first injection, an additional 111 MBq of ^{123}I-IMP was injected. Data were collected in a continuous rotating mode in reciprocal directions at 20 seconds per revolution for 66 minutes from 96 directions. The transaxial images were reconstructed using a filtered back projection algorithm and a Butterworth prefilter. Resting and vasodilated perfusion images were obtained using the subtraction technique. Data were formatted as a 3-dimensional (3D) dataset with 64 × 64 × 64 cubic voxels, 4 mm per voxel side.

PET Imaging

A Headtome V/SET 2400W system (Shimadzu Co., Ltd., Kyoto, Japan) was used for the PET imaging. Prior to the emission scan, a Ge-68/Ga-68 transmission scan was performed for 10 minutes for attenuation correction. All scans were performed at a resolution of 3.7 mm FWHM in the transaxial direction and at 5 mm in the axial direction. Images were reconstructed using an ordered subset expectation maximization algorithm (12 iterations with 4 ordered subsets). The subject's head was fixed in place with a head holder and was positioned using light beams to obtain transaxial slices parallel to the OM line. Data were formatted as a 3D dataset with 63 slices (3.17 mm thick) in 128 × 128 matrices. CBF, $CMRO_2$, OEF and CBV were measured using the conventional O-15 gas steady-state method.

Data Analysis

The SPECT and PET data were analyzed using an image analyzing software system (Dr. View Pro 5.0, Asahi Kasei Joho System Ltd., Tokyo, Japan). The SPECT and PET image data sets were displayed side by side, and regions of interest (ROIs) were drawn at corresponding positions in both images.[14] Multiple circular ROIs (20 mm in diameter) were placed in the cortical ribbon, basal ganglia, and white matter. ROIs in multiple slices from the basal ganglia level to the centrum semiovale level were linked together into four areas: the ACA territory, MCA territory, basal ganglia territory, and white matter.

The cerebrovascular reserve (CVR) was calculated from the SPECT data using the following equation: CVR

= (ACZ challenge count – resting count) × 100 /resting count.

All data were expressed as the mean ± 1SD. Differences in the mean values of the groups were analyzed using a one-way ANOVA followed by Bonferroni's multiple comparison. Differences were considered to be significant when the statistical p value was under 0.05.

RESULTS

Table 2 presents the individual findings of cerebral angiography. The main routes of collateral circulation in extensive BMV hemispheres were BMVs and leptomeningeal anastomoses. On the other hand, in diminished BMV hemispheres, transdural anastomosis was predominant, while leptomeningeal anastomoses were less developed. The feeders of those transdural anastomoses in the ACA territory were the anterior falx artery and middle meningeal artery, and those in the MCA territory were the middle meningeal artery. In three diminished BMV hemispheres (Pt No. 5, 6, 9), the left ACA or MCA periphery was filled by developed basal thin channels. Of these three hemispheres, one (Pt No. 5) had neither leptomeningeal nor transdural anastomoses.

Figure 2 shows the CBF, $CMRO_2$, OEF, CBV, CBF/CBV, and CVR as measured using PET and SPECT. In the extensive BMV group, the CBF and $CMRO_2$ in the ACA territory and the MCA territory were significantly lower than those in the other groups. The regional OEF in the ACA territory and the MCA territory was significantly higher in the extensive BMV group than in the normal controls.

No significant differences in the CBF, $CMRO_2$, or the OEF in the basal ganglia or white matter were seen among the groups, except for the CBF in the white matter.

Large differences in the CBV and the CBF/CBV were seen among the groups. In all the regions examined, the extensive BMV group showed a significantly higher CBV and a lower CBF/CBV than the other groups. The CVR was significantly lower in the extensive BMV group than in the normal controls in all the regions examined.

In contrast, no significant differences in any of the PET measurements were seen between the normal control group and the diminished BMV group, except for the CBF in the white matter.

DISCUSSION

The present study on the hemodynamic and metabolic impairments in adult patients with ischemic moyamoya disease shows that the hemodynamic status of hemispheres with extensive BMV is different from that of hemispheres with diminished BMV. Transdural, rather than intracerebral, collaterals were effective for maintaining cerebral circulation in the territory of the occluded ICA.

In contrast to pediatric patients, adult patients with moyamoya disease often develop intracerebral hemorrhage. To evaluate the hemodynamics in adult ischemic moyamoya disease, the present study excluded patients with hemorrhagic episode because the hemodynamics in hemorrhagic cases might be different from those in ischemic cases. In some previous papers, it was reported that CBF and CVR were not impaired in moyamoya patients with hemorrhagic onset. From this point of view, the results of this study may not apply to adult hemorrhagic moyamoya disease.

BMV, leptomeningeal anastomosis between the PCA and anterior circulation, and transdural anastomosis between the extracranial and intracranial vessels are the main routes of collateral circulation in patients with moyamoya disease. Mugikura et al. reported that leptomeningeal collaterals developed most when prominent BMVs are present. In the advanced angiographic stage, the degree of leptomeningeal collaterals from the PCA decreases as the steno-occlusive lesion extends to the PCA.[12] The transdural anastomoses, represented by ethmoid moyamoya and vault moyamoya vessels, develop later in the advanced angiographic stage.[15,16]

In the present study, we classified the patients into two subgroups: patients with extensive BMVs and retrograde filling of long-penetrating medullary arteries and patients with poor BMVs and no retrograde filling of long-penetrating medullary arteries. The former group corresponded to stage III and the latter to stage IV (minimization of moyamoya vessels) and stage V (reduction of moyamoya vessels) in Suzuki's angiographic classification.[2]

The most important finding of the present study was that the patients with extensive BMV hemispheres exhibited impaired perfusion and metabolism in the cortices whereas patients with diminished BMV hemispheres did not. The exception was the white matter area in the diminished BMV group. The mean CBF in the area was significantly more reduced than that in the normal control group. This may be explained by the fact that patients in the diminished BMV group had multiple lacunar infarctions as revealed by MRI.

Our results suggested that intracerebral anastomoses may not provide an adequate blood supply to the cerebral cortices, even if they are fully developed. Diminished BMVs were associated with well-developed transdural anastomoses in our patients. Based on these findings, we speculate that transdural collateral channels are more efficient in supplying blood, than intracerebral anastomoses, but develop gradually when BMV is minimized in adult patients with moyamoya disease. From this point of view, the formation of BMVs may be accelerated by persistent cortical ischemia. This speculation is supported by some previous reports[10,17–19] describing that STA-MCA anastomosis improved CBF in adult patients with moyamoya disease. It was also reported that STA-MCA anastomosis reduced BMVs, as revealed by follow-up

angiography studies, and decreased the risk of hemorrhage.

The purpose of STA-MCA anastomosis differs according to the type of adult moyamoya disease. In patients with ischemic onset, the purpose of STA-MCA anastomosis is the suppression of ischemic attacks by improving the cortical hemodynamic impairment. Such improvement in the cortical hemodynamics then induces reduction of BMV. In patients with hemorrhagic onset, things are different with the purpose of the anastomosis being the prevention of rebleeding by reducing the hemodynamic stress on BMV. The anastomosis, instead of BMV, supplies blood to the cortex to reduce BMV. As there is no evidence about the effect of STA-MCA anastomosis on the risk of rebleeding, the Japanese adult moyamoya trial (JAM trial) is now ongoing in Japan.

Cerebral oxygen metabolism is significantly decreased in extensive BMV hemispheres. Kuwabara et al.[8] reported no significant reduction in $CMRO_2$ in pediatric moyamoya patients with BMV. We speculate that the reduction in oxygen metabolism in adult patients may be induced by persistent oligemia for several years. Such metabolic impairment may be improved by the development of transdural and leptomeningeal collateral channels, as found in our subgroup with diminished BMV hemispheres associated with well-developed transdural collaterals. This speculation is supported by some previous reports showing that in pediatric patients, ischemic symptoms diminished in parallel with the development of ethmoid and vault moyamoya vessels[2] and the intelligence of pediatric patients with moyamoya disease could be improved by revascularization surgery.[4] Even in adult moyamoya disease, the reduction in $CMRO_2$ can be improved by a successful STA-MCA bypass surgery.[10]

In conclusion, severe hemodynamic and metabolic impairments were found in adult patients with ischemic moyamoya disease when the extensive development of basal moyamoya vessels persists. The severity of these cerebral hemodynamic and metabolic impairments in adults with ischemic moyamoya disease highly depends on the type of remaining collateral circulation. Extensive development of basal moyamoya vessels is a sign of severe hemodynamic impairment in adults with ischemic moyamoya disease. The results of the present study may be limited to adult patients with ischemic onset, and may not apply to those with hemorrhagic onset.

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Relationship Between C-Reactive Protein and Progression of Early Carotid Atherosclerosis in Hypertensive Subjects

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Background and Purpose—Hypertensive outpatients were investigated for C-reactive protein (CRP) and carotid atherosclerosis because the influence of CRP on the progression of subclinical atherosclerosis in hypertensives remains unclear.

Methods—A total of 124 outpatients (aged 40 to 79 years) in treatment for hypertension were enrolled. They underwent repeated ultrasonographic evaluation of the carotid arteries for 35±12 months. Focal intima-media thickening of ≥1.1 mm was defined as plaque, and the plaque number, plaque score, and the sum of all plaque thickness were calculated.

Results—Multivariate linear regression analysis revealed that CRP, pulse pressure, and systolic blood pressure were related to the annual change of plaque number (β=0.34, 0.27, and 0.30; all $P<0.01$) and plaque score (β=0.38, 0.27, and 0.23; $P<0.001$, $P<0.01$, and $P<0.05$, respectively) independently of other risk factors. In 64 patients taking antihypertensive medications with a blood pressure of <140/90 mm Hg, CRP and the pulse pressure were related to the annual change of plaque number (r=0.40 and 0.26; $P<0.01$ and $P<0.05$, respectively) and plaque score (r=0.44 and 0.31; $P<0.001$ and $P<0.05$, respectively).

Conclusions—In hypertensive patients being managed by drug therapy or lifestyle modification, CRP is an equivalent or superior independent predictor of the progression of carotid atherosclerosis than the pulse pressure or systolic blood pressure. (***Stroke.*** **2004;35:1625-1630.)**

Key Words: atherosclerosis ■ hypertension ■ carotid artery ■ inflammation ■ ultrasonography

Hypertension is 1 of the major traditional risk factors for atherosclerosis. The management of hypertension is very important, but its treatment and that of other traditional risk factors does not completely inhibit the development of atherosclerosis or prevent cardiovascular events.[1] Atherosclerosis is now considered to be partly attributable to an inflammatory response,[2] and there is evidence of a link between atherosclerosis[3,4] or cardiovascular disease (CVD)[5,6] and elevated serum levels of C-reactive protein (CRP). With regard to the contribution of CRP to the relationship between hypertension and CVD, a recent study showed that the risk of myocardial infarction was marginal in hypertensives without a simultaneous high CRP level.[7] Several other inflammatory serum proteins are reported to be associated with an increased risk of stroke among men with a high systolic blood pressure (SBP).[8] New guidelines suggest that patients who have an intermediate risk of CVD based on traditional risk factors may benefit from the measurement of high-sensitivity CRP (hs-CRP).[9] However, there have been no reports about the influence of CRP on the progression of subclinical atherosclerosis in patients with hypertension. It is well known that the severity of carotid atherosclerosis is closely related to the presence of CVD and the risk of CVD events. In the present study, we tested hs-CRP and office blood pressure as predictors of the progression of carotid atherosclerosis in hypertensive patients.

Materials and Methods

Patients

Between September 1996 and March 1998, we examined outpatients aged 40 to 79 years who were attending the Department of Internal Medicine and Therapeutics at Osaka University Hospital for carotid atherosclerosis because of the presence of risk factors for CVD. Each patient gave written informed consent to the collection of blood samples and follow-up for at least 2 years to evaluate the development of carotid atherosclerosis. Patients were excluded from the study if they had experienced a cardiovascular event during the previous year (n=2) or if they had advanced carotid atherosclerosis (n=25) or other diseases that could increase the hs-CRP level (18 had aortitis, 2 had collagen diseases, 2 had malignant tumors, and 1 had chronic bronchitis). During the follow-up period, 8 patients experienced a new cardiovascular event, 5 of whom did not undergo follow-up carotid ultrasonography. Another 5 patients developed malignant tumors, and 2 patients were lost to follow-up. A total of 12

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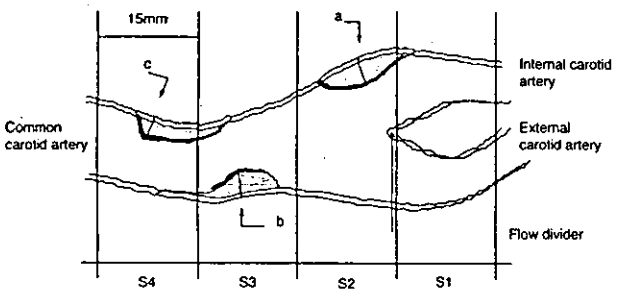

Figure 1. Diagram of carotid bifurcation and plaque score measurement obtained from B-mode ultrasonography. Plaque score was calculated by summing all plaque thicknesses in millimeters in each segment on both sides (a+b+c+contralateral plaques). Carotid artery was divided into 4 parts of 15 mm in length each from the flow divider (S1 to S4).

patients without follow-up carotid ultrasonography were deleted from the analysis. Ultimately, 179 patients were enrolled in the previous study, of whom 129 patients were hypertensives being treated with drug therapy or lifestyle modification. Information about antihypertensive therapy was missing for 5 patients, so this study presents data on the remaining 124 patients.

Risk Factors

Blood pressure was measured in the right arm with the patient in the seated position after a 5-minute rest, following recommendations of the American Heart Association.[10] The average of 2 consecutive blood pressure measurements was calculated. Hypertension was defined as an SBP of ≥140 mm Hg, a diastolic blood pressure (DBP) of ≥90 mm Hg, or current use of antihypertensive medications. The other traditional risk factors for CVD were classified as follows. Hypercholesterolemia was defined as a total cholesterol level of ≥220 mg/dL (5.69 mmol/L) or current cholesterol-lowering therapy. Diabetes mellitus was defined as a glycosylated hemoglobin A_{1c} concentration of >5.8% or current use of oral hypoglycemic agents. Body mass index was the weight in kilograms divided by the square of the height in meters. Patients were categorized as smokers if they were current smokers or had stopped smoking <1 month before entry into the study. Cigarette pack years were calculated for each patient as a measure of cumulative smoking exposure. Patients were categorized as having CVD if there was a history of cerebrovascular disease, ischemic heart disease, aortic aneurysm, or peripheral vascular disease.

Evaluation of Carotid Atherosclerosis

To evaluate the progression of carotid atherosclerosis, high-resolution B-mode ultrasonography using a 7.5-MHz duplex probe (EUB-525, Hitachi) was performed repeatedly over a period of ≥2 years. Baseline and follow-up ultrasound images were recorded on VHS videotape, and the changes of each plaque were evaluated in a blinded manner. The method was similar to that used by us in another prospective study.[3,11] On the basis of our previous findings, the upper limit of normal for the intima-media thickness (IMT) was set at 1.0 mm, and areas with an IMT of ≥1.1 mm were defined as atheromatous plaques. The plaque score was calculated by summing the thickness of all plaques measured in both carotid arteries (Figure 1),[12] and we used the number of plaques and the plaque score to estimate the severity of carotid atherosclerosis. The progression of atherosclerosis was estimated by inserting each parameter into the following formula: Δ value/year=(final value−baseline value)/years of follow-up. Advanced carotid atherosclerosis was defined as a plaque score of >10,[11] and such patients were not enrolled in this study.

Measurement of the Circulating hs-CRP Concentration

Blood samples were collected in tubes containing citric acid and stored at −80°C after centrifugation. The stored serum for each patient was thawed in April 1998 for hs-CRP measurement using an automatic immunonephelometer with a sensitivity of 0.02 mg/dL (Behring NA latex CRP; Behring Institute).

Statistical Analysis

Natural log transformation of the hs-CRP data achieved a normal distribution, so log-transformed hs-CRP values were used. All hs-CRP concentrations below the detection limit were assigned a log-transformed value of −4.605 (ie, an hs-CRP value of 0.01 mg/dL). The relationship between measured risk factors, including log-transformed CRP values, and the parameters of carotid atherosclerosis was evaluated by calculation of Pearson correlation coefficients. Spearman rank correlation coefficients were used for the skewed distribution of cigarette pack years. Student t test was used to evaluate the difference between the parameters in relation to the presence and absence of categorized traditional risk factors, including treatment with statins, aspirin, or angiotensin-converting enzyme (ACE) inhibitors. Multiple linear regression analyses were performed to assess the contribution of CRP to the prediction of annual changes of each parameter compared with the contribution of hypertension and other traditional risk factors. Two-way ANOVA with Newman–Keuls test was used to estimate between-group differences of parameters of carotid atherosclerosis in relation to hs-CRP and blood pressure. Probability values (2-tailed) of <0.05 were considered significant. For 2-way ANOVA test, Statistica for Windows R 5.5 (StatSoft) was used. The other statistical analyses were performed with SPSS for Windows version 9.0J.

Results

The baseline characteristics of the 124 subjects are summarized in Table 1. The follow-up period was 35±10 months. With regard to the relationships between hs-CRP and traditional risk factors, there was a significant association of the hs-CRP level with age (r=0.22; P<0.05), fasting blood glucose (r=0.19; P<0.05), and high-density lipoprotein cholesterol (r=−0.19; P<0.05). The relationship of CRP with cigarette pack years (r=0.17; P=0.059), pulse pressure (r=0.17; P=0.060), and SBP (r=0.15; P=0.086) was also positive but showed no statistical significance. There was no significant relationship between the hs-CRP level and the other traditional risk factors. Sex and the presence or absence of risk factors and treatment with ACE inhibitors, statins, or aspirin had no significant influence on the hs-CRP levels.

Among categorized risk factors, men had further progression than women (0.76±1.18 versus 0.43±1.00 in annual change of plaque score; P<0.05). The relationships between hs-CRP, pulse pressure, SBP, DBP, and the parameters of carotid atherosclerosis are shown in Table 2. Pulse pressure, SBP, and hs-CRP were correlated with the annual changes of plaque number and plaque score in simple regression analysis, and the correlations remained significant after adjusting for the effect of other traditional risk factors and for the baseline severity of carotid atherosclerosis. No other traditional risk factors (including DBP) were significantly correlated with the parameters of carotid atherosclerosis in simple regression analysis. When analysis was limited to the patients without hypercholesterolemia, diabetes mellitus, or current smoking, the results were similar to those in the total patient population, except that there was no significant association with SBP in the nonhypercholesterolemic or nondiabetic subgroups (Table 2). The progression of carotid atherosclerosis in relation to pulse pressure/SBP and hs-CRP is shown in Figures 2 and 3, respectively. Patients were divided into 2

TABLE 1. Baseline Characteristics of the Patients (n=124)

Age, y	62.7±8.7
Male	66 (53)
Antihypertensives medication	102 (82)
ACEI/CCB/β-blocker	33 (27)/74 (60)/37 (30)
α-blocker/diuretics	11 (9)/5 (4)
SBP/DBP, mm Hg	139±16/83±11
Pulse pressure, mm Hg	56±15
Hypercholesterolemia/statin medication	48 (39)/26 (21)
Total/HDL cholesterol, mg/dL (mmol/L)	205±31/58±15 (5.3±0.8/1.5±0.4)
Diabetes mellitus/oral hypoglycemic agents	21 (17)/4 (3)
Fasting blood glucose, mg/dL (mmol/L)	104±29 (5.8±1.6)
Hemoglobin A_{1c}, %	5.3±0.8
Body mass index, kg/m²	23.7±2.8
Current smoker	14 (11)
Cigarette pack years	0 (0, 6.0) [10.0]
History of CVD	36 (29)
Antiplatelet medication/aspirin medication	25 (20)/7 (6)
CRP, mg/dL	0.07 (0.04, 0.15)
Plaque No.	1.0 (0, 3.0) [2.4]
Plaque score	2.4 (0, 4.5) [3.9]

The age, blood pressure, cholesterol, fasting blood glucose, hemoglobin A_{1c}, and body mass index are shown as mean±SD. Data on the blood pressure, cholesterol, fasting blood glucose, and hemoglobin A_{1c} are shown for all 124 patients. Cigarette pack years, CRP, plaque no., and plaque score are shown as the median and interquartile range. The mean values of cigarette pack years for past and current smokers and the mean plaque no. and plaque score for the patients with carotid atherosclerosis are shown in square brackets. Other values are the no. of patients, along with the proportion in parentheses.

ACEI indicates ACE inhibitor; CCB, calcium channel blocker.

TABLE 2. Association Between hs-CRP, Blood Pressure, and Parameters Associated With the Development of Carotid Atherosclerosis

		Simple Regression		Multivariate Regression* (Standardized)	
		r	*P*	β	*P*
In total patients (n=124)					
ΔPN/yr	hs-CRP	0.314	<0.001	0.343	0.001
	Pulse pressure	0.281	0.002	0.267	0.006
	SBP	0.290	0.001	0.299	0.001
	DBP	0.054	0.557	0.000	0.999
ΔPS/yr	hs-CRP	0.328	<0.001	0.376	<0.001
	Pulse pressure	0.287	0.001	0.268	0.005
	SBP	0.238	0.008	0.227	0.014
	DBP	−0.031	0.736	−0.104	0.299
ΔPS/yr per subgroup					
Patients without hypercholesterolemia (n=76)					
hs-CRP		0.343	0.002	0.452	0.001
Pulse pressure		0.274	0.017	0.282	0.034
SBP		0.210	0.068	0.148	0.235
Patients without diabetes mellitus (n=103)					
Hs-CRP		0.283	0.004	0.424	<0.001
Pulse pressure		0.256	0.009	0.326	0.004
SBP		0.180	0.070	0.185	0.080
Noncurrent smoker (n=110)					
Hs-CRP		0.258	0.006	0.310	0.005
Pulse pressure		0.316	0.001	0.331	0.002
SBP		0.268	0.005	0.391	0.002

ΔPN/yr indicates annual change of plaque number; ΔPS/yr, annual change of plaque score.

*Each parameter of blood pressure, together with hs-CRP and other traditional risk factors, was used as an independent variable in each multivariate regression model. The standardized β and *P* values of hs-CRP in Table 2 are adjusted for pulse pressure, age, sex, total cholesterol, hemoglobin A_{1c} cigarette pack years, body mass index, the severity of carotid atherosclerosis, and uses of ACE inhibitor, statin, and aspirin. When SBP or DBP was used instead of pulse pressure as a parameter of blood pressure, the standardized β and *P* values of hs-CRP were similar to those in Table 2. hs-CRP indicates high sensitivity C-reaction protein; ΔPS/y, annual change of plaque score.

groups at the median pulse pressure (53 mm Hg), an SBP of 140 mm Hg, and an hs-CRP value of 0.12 mg/dL. We reported previously that annual rate of increase in carotid atherosclerosis was accelerated in patients with an hs-CRP value of ≥0.12 mg/dL.[3] Patients with higher hs-CRP levels had greater progression of atherosclerosis than those with lower hs-CRP levels in both the lower and higher pulse pressure groups and even in patients with an SBP of <140 mm Hg on antihypertensive therapy. When analysis was limited to the 64 patients with blood pressure of <140/90 mm Hg on antihypertensive therapy, the relationship between hs-CRP and carotid atherosclerosis was stronger than that for pulse pressure. There were no significant relationships between the other traditional risk factors (including SBP and DBP) and the annual changes of plaque number or plaque score, except for body mass index (Table 3).

Discussion

This is the first study to demonstrate that evaluation of CRP could be equal or superior for predicting the development of carotid atherosclerosis to measurement of the pulse pressure or SBP in hypertensives and that its predictive value is independent of blood pressure. With respect to the association between blood pressure and carotid atherosclerosis, to the best of our knowledge, there have been few longitudinal studies focused on the middle-aged and elderly population.[13,14] These studies have emphasized an elevated pulse pressure and SBP as risk factors for atherosclerosis. Similar to the results of such studies, our findings suggested that pulse pressure and SBP are related to the progression of carotid atherosclerosis. It is thought that an elevated pulse pressure causes greater stretching of the arteries, which induces fatigue and fracture of the elastic elements and thus is likely to hasten the development of intimal damage that leads to atherosclerosis.[15] The Framingham study demonstrated a link between cardiovascular mortality and pulse

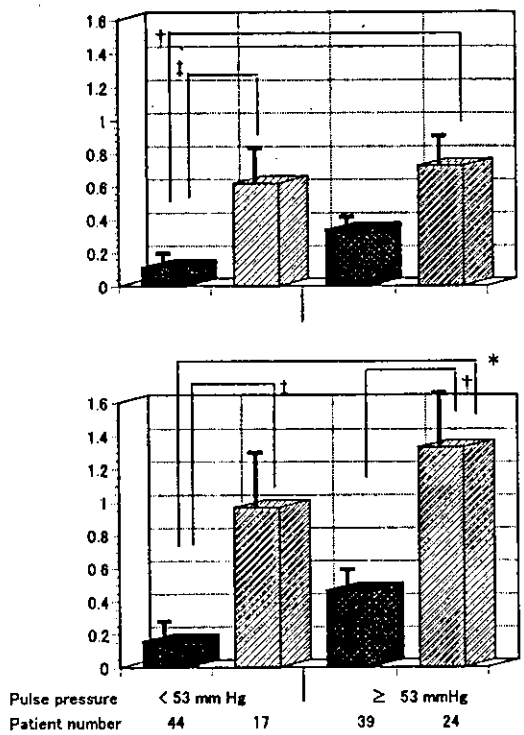

Figure 2. The annual changes of plaque number (top) and plaque score (bottom) in relation to pulse pressure and hs-CRP. ▨hs-CRP ≥0.12 mg/dL. ■hs-CRP< 0.12 mg/dL. Bars represent mean values and lines represent the SEM. *P<0.001; †P<0.01; ‡P<0.05.

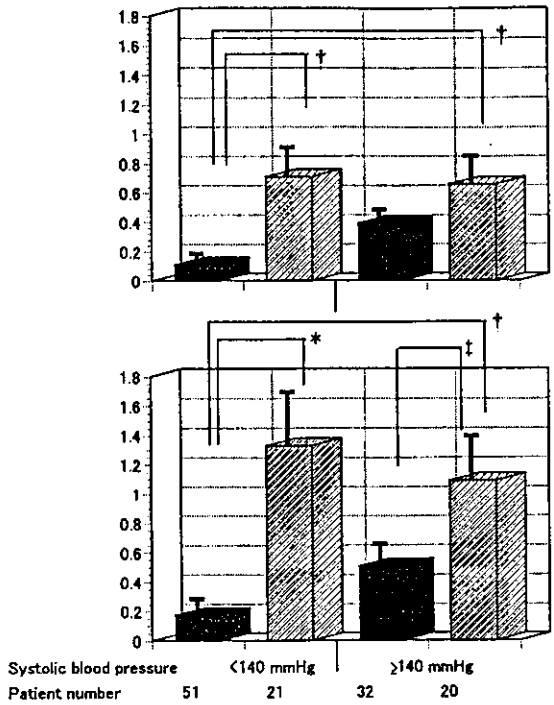

Figure 3. The annual changes of plaque number (top) and plaque score (bottom) in relation to SBP and hs-CRP. ▨hs-CRP ≥0.12 mg/dL. ■hs-CRP< 0.12 mg/dL. Bars represent mean values and lines represent the SEM. *P<0.001; †P<0.01; ‡P<0.05.

pressure by longitudinal follow-up of persons >50 years old.[16] Another large-scale study revealed similar results in male subjects aged 40 to 69 years,[17] whereas the age of the present study population was similar. We found that there was no significant relationship between the other traditional risk factors (including DBP) and the progression of carotid atherosclerosis. The lack of an association with these risk factors in the present study can be partly explained by the influence of drug therapy and lifestyle modification or the low statistical power of our analysis. The age of the present study population may also help to explain the lack of an association between DBP and carotid atherosclerosis.

Multivariate analysis revealed that CRP was one of the independent predictors of the progression of carotid atherosclerosis. Subset analysis excluding each traditional risk factor showed a similar result. One possible reason that a high CRP level is associated with carotid atherosclerosis indepen-

TABLE 3. Association Between hs-CRP Concentration, Blood Pressure, and Parameters Associated With the Development of Carotid Atherosclerosis in 64 Hypertensive Patients With Blood Pressure of <140/90 mm Hg on Antihypertensive Therapy

	Simple Regression			
	ΔPN/yr		ΔPS/yr	
	r	P	r	P
hs-CRP	0.404 (0.23, 0.91)	0.002	0.436 (0.48, 1.80)	<0.001
Pulse pressure	0.264 (0.015, −0.34)	0.044	0.310 (0.05, −1.8)	0.016
SBP	0.225	0.086	0.237	0.069
DBP	−0.007	0.958	−0.040	0.761
Age	−0.198	0.134	−0.183	0.162
Total cholesterol	0.078	0.558	0.011	0.931
Hemoglobin A_{1c}	−0.021	0.882	−0.016	0.907
Cigarette pack years	0.004	−0.977	0.012	0.930
Body mass index	0.334 (0.048, −0.73)	0.010	0.272 (0.12, −2.36)	0.035

ΔPN/yr indicates annual change of plaque number; ΔPS/yr, annual change of plaque score. The values in parentheses show the regression coefficient and intercept.

dently of blood pressure and other traditional risk factors may be the tight linkage of CRP with atherosclerotic processes. For example, CRP may contribute to monocyte recruitment in atherogenesis[18] and to induction of tissue factor release by monocytes, which is potentiated by interferon-γ and lipopolysaccharide.[19] CRP has a direct influence on atherosclerotic vessels by activation of the complement system, thereby promoting inflammation and thrombosis.[20] A recent clinical study showed that CRP was significantly correlated with the calculated 10-year Framingham coronary heart disease risk (FCHDR) but was weakly correlated with most individual components of the FCHDR score.[21] This suggested that CRP may capture different components than the traditional components of coronary risk reflected in the FCHDR score. Thus, monitoring of the blood pressure is important but not enough to predict the development of atherosclerosis in hypertensives. The average of 2 consecutive office blood pressure measurements at 1 time point was representative of the blood pressure value in the present study. A recent study suggested that circadian SBP variability is the best independent predictor of the development of carotid atherosclerosis,[13] whereas a cross-sectional study revealed that target organ damage caused by hypertension is more closely related to the home blood pressure than the office blood pressure.[22] The serum level of CRP may partly reflect the circadian blood pressure pattern or home blood pressure, or may be an indicator of a step in the process of atherosclerosis itself,[9] making it equal or superior to office blood pressure measurement for the prediction of atherosclerosis.

Chronic inflammation may induce endothelial dysfunction, which is followed by further elevation of blood pressure (pulse pressure and SBP)[23] and the onset of cardiovascular disease.[24] Several studies have shown that CRP is an independent risk factor for hypertension,[25,26] so CRP, inflammation, and hypertension appear to be linked in the process of atherosclerosis. A recent study suggested that inflammation is important for accelerated progression of atherosclerosis, particularly in hypertensives.[8] Although the relationship of CRP with pulse pressure and SBP was positive in the present study, it did not reach statistical significance. This lack of a significant association might be attributable to the low statistical power of our analysis or use of antihypertensive medication by the subjects,[27] or it may indicate that the actual association is weak.[21]

It could be argued that our results were influenced by a selection bias of the patient population because most of them were on antihypertensive therapy and some had other traditional risk factors. However, the relationship of pulse pressure, SBP, and CRP with carotid atherosclerosis remained significant after adjusting for antihypertensive therapy and other traditional risk factors, and stratified analysis showed similar results. Recent guidelines have proposed that the entire adult population should not be screened for CRP measurement for purposes of cardiovascular risk assessment but that the measurement may be useful in selected patients, such as those estimated to have a moderate risk on the basis of the 10-year FCHDR.[9] The risk management in the present study population was similar to the FCHDR concept of moderate risk, and we demonstrated that CRP was equal or superior to the office blood pressure for predicting the progression of carotid atherosclerosis, with these parameters being independent of each other. In conclusion, measurement of CRP may be valuable for predicting the progression of carotid atherosclerosis in selected hypertensive patients who are already being treated by drug therapy or lifestyle modification.

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<原　著>

超急性期入院虚血性脳血管障害の通常治療による3カ月目の転帰
—脳卒中急性期患者データベースによる前向き検討—

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要旨：目的：超急性期入院虚血性脳血管障害の通常治療による3カ月目の転帰を検討する．

方法：発症3時間以内に入院し，通常治療を受けた入院時NIH Stroke scale 5～30の虚血性脳血管障害患者で，脳卒中データベースに登録され，発症後3カ月予後を前向きに追跡調査し得た312例（平均73.5歳）を対象とした．機能予後はmodified Rankin scale（mRS）で評価した．

結果：全体では3カ月後mRS 0～1群が21%，2～3群が24%，4～5群が44%，死亡が11%であった．重症度別では入院時NIHSSが5～9では3カ月後のmRS 0～1が40%，10～14では13.6%，15～20では3.3%，21以上では3.6%とNIHSS15以上では極めて予後不良であった．

結論：中等症虚血性脳血管障害患者では超急性期に入院しても，通常治療のみでは社会復帰レベルまで回復する頻度は比較的低いことが示された．

Key words: stroke databank, Japanese standard stroke registry study, acute ischemic stroke, 3 month outcome, non-thrombolytic therapy

（脳卒中 26：323—330，2004）

はじめに

脳梗塞とくに心原性脳塞栓は主幹脳動脈閉塞による急性虚血が原因であり，その根本的治療として長い間その閉塞部再開通療法が模索されてきた．1995年に米国National Institute of Neurological Disorders and Stroke（NINDS）による組織プラスミノゲンアクチベーター（rt-PA）の発症3時間以内超急性期脳梗塞に対する臨床試験が実施され，初めてrt-PAの有効性が認められた[1)]．1996年に米国で許可され，脳梗塞の超急性期医療の第一選択として，すでに30カ国で認可され普及しつつある．我が国でも実は同時期に発症6時間以内の心原性脳塞栓による中大脳動脈閉塞例を対象にrt-PA静注による血管撮影を用いた臨床試験が実施され，有意な改善が確認されたため，当時の厚生省に申請していたが，特許問題で取り下げた経緯がある．最近，ようやく我が国でもrt-PAの臨床試験が実施され，近い将来に保険適応になる可能性がみえてきた．

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